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(54) **Novel poly-esters, their preparation and pharmacolgical use thereof**

(57) The invention provides a polyester of a polyol, said polyol containing at least 3 hydroxyl groups and having a molecular weight of up to 20,000 at least 1 hydroxyl group in said polyol being in the form of an ester, with a poly- or copoly-lactic acid residue, each having a molecular weight of at least 5,000.

The polyester is useful for parenteral depot formulations containing a pharmacologically active agent such as bromocriptine, ketotifen or co-dergocrine.

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SPECIFICATION

Novel esters, their preparation and use

The invention relates to novel esters, especially polyol esters, with polymeric hydroxycarboxylic ester residues, their preparation and use e.g. in the production of depot forms of pharmacologically active agents.

A broad class of polyol esters having polymeric hydroxycarboxylic ester residues are disclosed from the German Patent No. 1.020.034 in which glycerol esters having polylactide ester residue of 30 lactic acid residues or pentaerythritol ester with polylactic acid residue of 18 lactic acid residues are specifically described. The patent does not specifically disclose any longer chain polymer esters of polyols having at least three hydroxyl groups.

These products are used as solvents, e.g. for pharmaceutical purposes, as emulgators or as additives for synthetic materials and plastics. There is no disclosure of their use for pharmaceutical depot matrix compositions.

Esters from sugar alcohols, e.g. from erythritol, xylitol, ribitol and sorbitol with poly-ε-hydroxycapronic acid are described in Journal of Polymer Science, Polymer Chemistry Edition, Vol. 20, 319-326, especially at 323-326 (1982).

The molecular weight of these esters depends on the extent of esterification of the hydroxyl groups of the polyol esters and on the length of the poly-ε-hydroxycapronic acid residues. Its order of magnitude is from about 26000 to 65000.

The esters exhibit a star polymer structure, their single polyol residue as the central part being surrounded by acid residue chains. No use of the polyol esters is mentioned in the publication.

The diffusion velocity of pharmacologically active agents from the ester and the degradation velocity of the ester as a matrix material for active agents are too small for practical use as an implant or microcapsule. Due to the hydrophobic properties of the poly-ε-hydroxycapronic acid residues the esters are not suitabl as matrix materials for depot forms of pharmacologically active agents.

Several depot forms of pharmacologically active agents have been proposed in the literature. In the European application No. 92918, are disclosed polypeptides in a matrix of an ester of e.g. polyvinyl alcohol (M.W. 14000) or polyethylene glycol (M.W. 6000 or 20,000) containing polymer hydroxycarboxylic ester residues, e.g. from lactic acid (M.W. 26,000 to 114,000) and sometimes additionally glycolic acid (M.W. 10,000).

However, matrix materials having high molecular proportions of such polyol radicals have too hydrophilic properties and become degraded under use conditions too quickly.

Additionally, the strong hycrophilic properties and softness of the matrix materials hinder their production, the further processing and the use of depot forms, especially microcapsules.

As esters are additionally mentioned, e.g. dextrane as a polyol, but due to the high molecular weights of the dextranes such ester formation is practically impossible.

Depot forms of pharmacologically active agents in a matrix of a polymer of polyols and hydroxy carboxylic acids are proposed as part of a very broad class of products in the International application WO 78/00011 (PCT). However, polymers of polyol and hydroxy monocarboxylic acids are not exemplified. Exemplified are depot forms from a polyol ester containing polymeric dicarboxylic acid residues, e.g. of tartaric acid.

These polyol esters have a structure different from the products described above. They have a linear chain and contain alternatively polyol residues and dicarboxylic acid residues.

The formed esters have such a low solubility, and soluble precondensates must be formed in order to incorporate the pharmacologically active agents. Only then can the precondensated active agent containing matrix materials be condensed further.

If saturated dicarboxylic acids, such as tartaric acid are used, it is stated that the final total condensation must be carried out at an elevated temperature (about 170-200°C) which is not suitable for heat-sensitive active agents.

Using pentaerythritol as a polyol, strongly cross-linked products are formed, which are not suitable for incorporating pharmacologically active agents and which do not degrade in vivo sufficiently fast.

The mass degradation rate for depot formulations made from these materials is too slow.

The manufacturing process disclosed to produce the microcapsules or other depot forms is also tedious.

The known matrix polymers of the art generally have a disadvantageous short or long degradation period under conditions of use, e.g. in the body, compared with the required release period of the pharmacologically activ agent, causing the active agents either to disappear prematurely with the matrix material or to be disapp ared completely from the still present polymer matrix. Accordingly an additional dosage of the depot form cannot be administered subsequently, since an undesired accumulation of the polymeric matrix material may occur.

The pres nt invention sets out to overcome th above disadvantages and to provide a useful pharmaceutical depot form for clinical use.

Furthermore the depot forms made from the polyol esters according t the invention may have the advantage f a drug release time which is satisfactorily long, .g. 1 month, and a short degradati n peri d of th mass thereafter. They are suitable for the incorporation of a large variety of e.g. water soluble or hydrophobic active agents

Additionally, the poly l esters of the inventi n may be easy handled and be easily worked up to incorporate the active agents and to produce pharmaceutical composition forms, e.g. microcapsules and implants. These microcapsules are n t soft; consequently, they are easy to administer through an injection needle.

The present invention provides an ester of a polyol, said polyol containing at least 3 hydroxyl groups and having a molecular weight of up to 20,000 at least 1 hydroxyl group in said polyol being in the form of an ester, with a poly- or co-poly-lactic acid residue each having a molecular weight of from 5,000 e.g. to 85,000. In another aspect the present invention provides a reaction product of a polyol containing at least 3 hydroxyl groups and having a molecular weight of up to 20,000 or a reactive derivative thereof and lactic acid or a reactive derivative thereof and if desired at least a second hydroxycarboxylic acid or a functional derivative thereof, the product having a polymer chain of molecular weight of at least 5,000. These products are indicated as polyol esters of the invention.

The polyol residues are particularly of a polyol containing a chain of carbon atoms. A special polyol form is such having a linear structure and containing 3 to 6, particularly 6 hydroxyl groups. Suitable polyols having a linear structure include e.g. mannitol, pentaerythritol, sorbitol ribitol and xylitol. Another preferred polyol form is one having a cyclic structure and containing 4 to 30 hydroxyl groups.

The polyols of a cyclic structure contain particularly one or more saccharide units and with at least 3 hydroxyl groups per unit. Examples of such polyols are those with a fructose structure, e.g. fructose itself. Particular polyols with cyclic structure are those having glucose structure, e.g. glucose itself, or having 2 to 8 glucose units. These units are preferably connected in 1,4 and/or 1,6-position, especially in 1,4-position. A polyol containing more glucose units, connected in 1,4-position, is e.g. β-cyclodextrine.

The preferred polyol is glucose.

The polyol esters may have e.g. a polyol residue with at least 2 or 3 hydroxyl groups in the form of esters, which contain poly-lactide or co-poly-lactide chains. Their structures may be thus branched, i.e. star shaped. Preferably each such chain has the same hydroxycarboxylic acid residue.

The chains may contain lactide residues alone. Alternatively they may contain additionally e.g. one, two, three or more specific hydroxycarboxylic acid residues, e.g. up to 70 Mol%, e.g. 30-70%.

Preferred extra residues are glycolic acid residues. Preferably up to 70 Mol%, e.g. 30-70%, especially 50 Mol% glycolic acid units are present. Instead of or in addition to the glycolic acid units other different units may be present, e.g. ε-hydroxycapronic acid units, preferably up to 20 Mol%.

The lactic acid units may be present in optical pure form (D- or L-lactide form) or as their mixtures, e.g. their racemic form (D,L-lactide form).

The present invention also provides a process for the production of a product of the invention characterised in that a polyol of a molecular weight of up to 20,000 and having at least 3 hydroxyl groups or a reactive derivative thereof is esterified with lactic acid or a reactive derivative thereof or additionally with at least a second hydroxycarboxylic acid or a functional derivative thereof.

Preferably the process is characterised in that a polyol of a molecular weight of up to 20,000 and having at least 3 hydroxyl groups, is reacted with lactic acid or additionally with at least a second hydroxycarboxylic acid in lactone- or dimeric cyclic ester form, in the presence of a catalyst, which makes a ring opening polymerisation feasible.

The catalyst is preferably Sn-octoate.

The reaction components are e.g. mixed together with the catalyst and reacted at an elevated temperature.

If a solvent is present, e.g. toluene, the components may be reacted at the reflux temperature of the solvent. Without a solvent the reaction temperature can be higher, e.g. if glucose is used as a polyol, up to about 170° and if β-cyclodextrine is used, up to 180°. Preferably the reaction is effected in the absence of water.

The formed polyol ester of the invention may be purified and isolated in a conventional manner.

The determination of the molecular weight of the purified product may be effected using conventional methods, preferably by gelpermeation-chromatography (GPC) using polystyrene as standard (Mw) Dupont Ultrastyragel R 500 Angstrom and 10000 Angstrom as the column and tetranydrofuran as a solvent at ro m temperature.

The molecular weights Mw of the polyol esters according to the invention are preferably between 20,000 and 200,000, e.g. between 20,000 and 80,000.

The molecular weights of the polyol esters of the invention are dependent on the weight ratio of the components in the reaction and on the reaction conditions, e.g. the reaction temperature (see Example 8). A lower reaction temperature may lead to shorter polymer chains and thus to lower molecular weight polyol esters.

The isolation and purification may influence the molecular weight of the purified polyol ester. Changing the isolati n and purification conditions leads to a change of the mol cular weight (see Example 2). Since the p lyol est r may exist generally in fact as a mixture of molecules with chains of a different length the composition of this mixture may b influenced by is lation and purification methods, such as extraction, filtration and the isolation and purification liquids and their amounts and the isolation and purificati n temp rature.

The molecular weight f th purified polymer may be increased by removing low m lecular weight comp unds, e.g. by a suitabl precipitation of the polymer, .g. in methanol, or by a membrane filtration.

The amount of components having lower molecular weights may be reduced by membrane filtration to such an extent, that in the molecular weight spectrum, determined by GPC, their peaks altogether have a height of up to 10%, preferably up to 7% of the height of the peak Mw f the polymer.

The invention thus also provides a product, wherein in the GPC any separate low molecular weight peaks comprise altogether up to 10% of the height of the peak Mw of the polyester.

The polyol esters of the invention are particularly suitable to incorporate active agents and produce sustained release effects of the active agents in the body.

The balance of hydrophobic and hydrophilic factors – the polyol residue represents the hydrophilic and the poly lactide or co-poly lactide residue the hydrophobic factor – can be regulated by changing the polyols, the extent of esterification of the hydroxyl groups, the chain length of the polymeric chains and the identity and the relative amounts of the specific hydroxycarboxylic acid units in the chain.

The polyol esters according to the invention are therefore particularly suitable for the preparation of pharmaceutical depot formulations containing pharmacologically active agents. Such depot formulations may exist as a polyol ester matrix containing the active agent. Preferred depot forms are implants (e.g. for subcutaneous administration) and microcapsules (e.g. for oral or particularly for parenteral, e.g. intramuscular administration).

The present invention therefore also provides a pharmaceutically depot form, having a matrix of the ester of the invention, containing a pharmacologically active agent.

The depot forms are novel and form part of the invention.

The depot forms may be made in conventional manner, the polyol esters according to the invention being easy to handle and often incorporating a high concentration of active agent.

In order to produce microcapsules, the active agent may be dissolved in a volatile solvent, such as methylene dichloride. A solution of the polyol ester, e.g. in the same solvent, may then be added and the resulting mixture may be sprayed into air while carefully regulating the temperature and then dried to form microcapsules.

Alternatively the active agent may be dissolved or suspended, e.g. in methylene dichloride, and the polyol ester may be dissolved in a volatile, water immiscible solvent, e.g. methylene dichloride, after which the organic phase may then be mixed vigorously with a stirred aqueous solution, e.g. buffered to pH 7, optionally containing e.g. gelatine as an emulsifier. The organic solvent may then be removed from the resultant emulsion and the resultant microcapsules be filtered off or separated by centrifuging, washed, e.g. in a buffer, and dried.

In order to produce implants the active agent may be mixed with the polyol ester and dissolved in a volatile solvent. The solvent may be evaporated and the residue ground up. An extrusion may be formed in conventional manner, which is then pressed e.g. as implant tablets of 5 to 15, especially 7 mm, and of 20-80 mg, e.g. 20-25 mg matrix material at 75°C and 80 bar during 10 to 20 min.

Depending on the active agent, the microcapsules may take up an average of up to 60 % by weight of the active agent. The implants are preferably prepared in such a manner that they contain up to 60, e.g. 1 to 20 %, by weight of the active agent.

For the active agent Bromocriptine, microcapsules may be prepared containing at most 25 %, especially up to 18 % and implants containing up to 18 % by weight of the active agent.

The microcapsules may have a diameter from a few submicron to a few millimeters. For pharmaceutical microcapsules diameters of at most about 250 microns, e.g. 10 to 60 microns, are strived for, in order to facilitate passage through an injection needle.

The depot formulation according to the invention may be used to administer a wide variety of classes of active agents, e.g. pharmacologically active agents such as contraceptives, sedatives, steroids, sulphonamides, vaccines, vitamines, anti-migraine drugs, enzymes, bronchodilators, cardiovascular drugs, analgesics, antibiotics, antigens, anti-convulsive drugs, anti-inflammatory drugs, anti-parkinson drugs, prolactin secretion inhibitors, anti-asthmatic drugs, geriatics and anti-malarial drugs.

The depot formulations may be used for the known indications of the particular active agent incorporated therein.

The exact amounts of active agent and of the depot formulation to be administered depends on a number of factors, e.g. the condition to be treated, the desired duration of treatment, the rate of release of active agent and the degradability of the polymer matrix.

The desired formulations may be produced in known manner. The amount of the pharmacologically active agent required and the release rate thereof may be determined on the basis of known in vitro or in vivo techniques, described e.g. in Examples 26-29, e.g. how long a particular active agent concentration in the blood plasma remains at an acceptable level. The degradability of the matrix may also be obtained by in vitro or especially in vivo techniques, for example wherein the amount of matrix materials in the muscle is weighed after particular time periods.

Th depot formulations of th invention may be administered in the form of e.g. microcapsules, e.g. orally preferably subcutaneously or intramuscularly, preferably in the form f or in a suspensi n in a suitabl liquid carrier or in the form of implants, e.g. sub-cutane usly.

Repeated administration of the depot formulations f the invention may be effected when the polyol ster matrix has suffici ntly degraded, e.g. after 1 month.

Examples of doses for the preferred c mpounds are:

For prolactin secretion inhibition with bromocryptine, for example an i.m. depot formulation may be produced which daily provides 2.5 to 7.5 mg bromocryptine over about 30 days and contains for example 70 to 230 mg bromocryptine mesylate.

For the treatment of bronchial asthma with ketotifen, for example an i.m. depot formulation may be produced which daily provides 0.5 to 0.8 mg ketotifen over about 30 days and contains for example 15 to 25 mg ketotifen.

For the reactivation of cerebral metabolism with codergocrine, for example an i.m. depot formulation may be produced which daily provides 0.1 to 0.4 mg co-dergocrine in about 30 days and contains about 3 to 12 mg.

Depot formulations for other active agents may be formulated in analogous manner, e.g. to provide the known appropriate, e.g. therapeutic, concentration of active agent for parenteral use over an extended period of time, e.g. 30 days.

As indicated above the polymer degradation may be followed in in vivo and in vitro experiments, described in Examples 24 and 25. It may be seen that the polyol esters of the invention degrade faster than corresponding known polylactide and poly-lactide/glycolide acids and especially a faster degradation may be seen in the early stage, e.g. up to 30 days, especially in the case of poly-lactide/glycolide polymer chains.

Membrane filtration results in residual polymer products having in general in the early stage, especially up to 30 days, a smaller mass degradation rate as that of the corresponding non-filtered product. In the cas of residual polyol esters of the invention, the degradation may be over 50% up to 30 days, and in the case of the Example 6 as described hereinafter about 70%. After 40 to 50 days it may be practically complete.

In in vitro and in vivo release rate tests the polyol esters of the invention may release the active agent at the same rate order as for corresponding known polymeric poly- or co-poly-lactides, e.g. in 30 days.

The active agents may be released mainly by diffusion from the matrix and only to a small extent by degradation of the matrix material.

This results in a more regular rate of release of active agent.

An advantage of the polyester matrices of the invention in that after a practically complete release of active agent they may be quickly degraded to an acceptable size, which may be transported by the body fluids from the site of administration.

Accordingly the present invention provides a parenteral pharmaceutical depot formulation for use as an implant or microcapsules containing a pharmacologically active agent embedded or encapsulated in a polymer matrix, said formulation being adapted to release all or substantially all the active material over an extended period of time and the polymer being adapted to degrade sufficiently to be transported from the site of administration within 20 days after release of all or substantially all the active agent.

In the following examples all temperatures are in degrees Centigrade and uncorrected.

HYFLO is a known filtering aid.

Polyol ester from D(+)-glucose, DL-dilactide and diglycolide

Example 1

79.4 g (0.684 Mol) of diglycolide, 120.6 g (0.838 Mol) of DL-dilactide and 0.4 g (2.2 mMol) of D(+)-glucose (0.2 %) were placed in a 1.5 l flask and heated, while stirring to 135° in an argon atmosphere after which 1 ml of Sn-octoate was added.

The reaction is exothermic. The temperature increases to 172°. After 5 minutes stirring is discontinued and the brown viscous mixture is reacted further at 130-140° for 17 hours. After cooling 500 ml of methylene dichloride was added. The mixture was dissolved as much as possible by boiling and the solvent was separated. This procedure was repeated after which the residue was extracted additionally with 500 methylene dichloride. The combined dark-brown solutions (in total 1500 ml) were purified with 50 g Hyflo, concentrated to 500 ml and treated with 500 ml of a 10% aqueous HCl-solution to remove the catalyst. The solution was washed five times with 500 ml of water to pH 4.5 and diluted to 1 l with methylene dichloride.

The solution was treated with $MgSO_4$ and with Hyflo, concentrated to 500 ml and added dropwise within half an hour to 3 l of methanol at −60°C. At this temperature the mixture was stirred for 3 hours. Then the product was filtered off and dried at 40°C in vacuo.

The molecular weight was determined by gel permeation chromatography (GPC):
Mw = 34 800 Mn = 19 600 Mw/Mn = 1.77
Acid number: 6.8
Non-reacted lactide: 1.7 %
Non-reacted glycolide: <0.4 %
Molar ratio glycolide/lactide in the polymeric chains: 45/55
NMR: 360 MHz; ($CDCl_3$)
5.20 (m, 0.55 H, -CH-lactic acid)
4.82 (m, 0.9 H, $-CH_2$-glycolic acid)
1.58 (m, 3 H, $-CH_3$-lactic acid)
IR: (CH_2Cl_2)
cm^{-1} 2950 (w,CH_3); 1760 (s,-COOR); 1390 and 1420 (w,CH_3); 1160 (s,-O-); 1090 (s,-O-).

Examples 2 - 5
In a manner analogous to that in Example 1, the following polyolester were prepared:

Ex.	*Polyol*	*DL-Di-lactide*	*Digly-colide*	*Sn-Octoate*	*React. temp.*	*Mw* / *Mn*	*Mw/Mn*	*Mol ratio lactide/glycolide*	*Acid number*	*Non reacted lactide and glycolide*
2*	4 mg C^{13}-D(+)-glucose (0,2%)	1.2 g	0.8 g	10 µl	–	31,400 17,300	1.81	–	–	–
3*	3.85 mg D(+)-glucose + 0.15 mg D(+)-$1C^{14}$-glucose	1.2 g	0.8 g	10 µl	–	26,400 10,600	2.50	–	–	–
4	0.2 g D(+)-glucose (0.2%)	60.3 g	39.7 g	0.5 ml	168°	34,600 20,700	1.67	55/45	5.7	0.6 % <0.4 &
5	0.2 g D(+)-glucose (0.2%)	60.3 g	39.7 g	0.5 ml	155°	23,600 13,300	1.77	58/42	8,0	<0,4 % <0,2 %

• For analytical purp ses, se following commentary.

Comments on Example 2

Prepared to show by analysis that the glucose was incorporated into the polymer and that indeed a polyolester was formed.

Measures were taken to intensify the NMR-signal of the glucose. The glucose was a C^{13}-uniform marked glucose with 98.3 atom percent C^{13} (LOT No.2358-4 MSD ISOTOPES, Merck, Canada).

The NMR-signal of the C^{13}-glucose starting material was compared with the signal of the C^{13}-glucose ester:

C^{13}-Glucose

NMR C^{13} ppm 97.13 (d,C-1β); 93.32 (d,C-1α); 77.63 (t,C-5β); 76.92 (t,C-3β); 75.57 (t,C-2β); 73.84 (t,C-3α); 72.92 (t,C-2α); 72.24 (t,C-5α); 71.07 (t,C-4α); 70.63 (t,C-4β); 61.95 (dxd, C-6αβ).

C^{13}-Glucose ester of Example 2

NMR C^{13} ppm 91.80 (m, C-1β); 89.84 (m, C-1α); 72.51 - 66.73 (m, C-2,3,4,5α,β); 62.90 (m, C-6).

Since the glucose signals all are broad multiplets, it is assumed, that the glucose was practically completely incorporated. Mol ratio lactide/glycolide/glucose = 32.3/66.7/0.2.

Comments on example 3

GPC-determination with simultaneous UV and radioactivity determination was used for the analysis of these products. It is observed that the radioactivity of the test sample is proportionally distributed over the whole range of molecular weights and that both the retention times in the UV and the radioactivity determinations are equal.

The radioactivity of the test sample is about 30 % of the predicted value, indicated that about 0.06 % f the glucose was incorporated (it was started with 0.2 %).

Example 6

The product of Example 4 was dissolved in methylene dichloride and purified by a membrane filtration under a pressure of 2 atm.

Amicon apparatus
Membrane: DDS 6000 MwCO
Type FS 81 PP
Flow velocity: 2,2 ml/min
The end volume was 2000 ml.

Residue *From NMR*

Mw = 42 200, Mn = 31 300, $\frac{Mw}{Mn} = 1.35$, $\frac{\text{lactide}}{\text{glycolide}} = \frac{53}{47}$ (Mol ratio)

Acid number 3.4

non reacted lactide <0.2 %
non reacted glycolide <0.4 %

Filtrate *From NMR*

Mw = 21 600, Mn = 13 600, $\frac{Mw}{Mn} = 1.58$, $\frac{\text{lactide}}{\text{glycolide}} = \frac{53}{46}$ (mol ratio)

Acid number 10.1

non reacted lactid 1.2 %
non reacted glycolide <0.4 %

Example 7

39.7 g (0.342 Mol) f diglycolide, 60.3 g (0.419 Mol) dilactide and 0.2 g (1.1 mMol) D(+)-glucose (0.2 %) and 40 ml of toluene are heated in a 750 ml flask, while stirring to boiling temperature (108°) after which 0.5 ml Sn-octoate are added. The reaction is slightly exothermic. The temperature was raised to 112°. After 3 hours stirring was discontinued and the brown viscous mixture was reacted further three days at 110°. After cooling 500 ml of methylene dichloride were added and the mixture was diluted at boiling temperature, purified with Hyflo and filtered.

The solution was evaporated to dryness, the residue dissolved in methylene dichloride and shaked with 400 ml of a 5 % aqueous HCl solution. The solution was washed four times with 400 ml of water to pH 5 and diluted to 1 l with methylene dichloride.

The solution was dried with $MgSO_4$ and evaporated to dryness in vacuo at 40°C. The residue was dried in vacuo at 40°.

Molecular weight: Mw = 32 200; Mn = 18 400; Mw/Mn = 1.75.

NMR and IR: As in Example 1.

Example 8

In a manner analogous to Example 7, the following polyolester was prepared in 345 ml of toluene.

Ex.	polyol	DL-dilactide	diglycolide	Sn-octoate	react. temp.	Mw / Mn	$\frac{Mw}{Mn}$	Mol ratio $\frac{lactide}{glycolide}$	acid-number	non reacted lactide/ glycolide
8	0.6 g D(+)-glucose (0.2%)	180.9g	119.1g	1.15 ml	114.1°	20,000 12,000	1.66	–	7.2	<0.1 % <0.4 %

Example 9

In an analogous mann r as describ d in Example 6 the following product was prepared by membrane filtration from the product of Example 8:

Flow velocity: 1 ml/min

The end volume was 2200 ml

Residue

Mw = 26 200, Mn = 18 000, $\frac{Mw}{Mn}$ = 1.45

From NMR

$\frac{\text{lactide}}{\text{glycolide}} = \frac{62}{37}$ (mol ratio)

Acid number 4.0

non reacted lactide <0.2 %
non reacted glycolide <0.4 %

Filtrate

Mw = 12 200, Mn = 3 300, $\frac{Mw}{Mn}$ = 3.75

From NMR

$\frac{\text{lactide}}{\text{glycolide}} = \frac{60}{40}$ (mol ratio)

Acid number 9.7

non reacted lactide <0.2 %
non reacted glycolide <0.4 %

Polyol ester from β-cyclodextrine, DL-dilactide and diglycolide

Example 10

26.1 g of diglycolide, 39.6 g of DL-dilactide and 0.635 g β-cyclodextrine were heated in a 500 ml flask, while stirring to 140°, in a nitrogene atmosphere after which 0.125 ml of Sn-octoate was added. The reaction is distinctly exothermic. The temperature was raised to 180°. After 10 minutes stirring was discontinued and the brown viscous mixture was reacted further at 140° for 17 hours.

The purification and isolation were carried out in an analogous manner as described in Example 1.

Molecular weight (GPC): Mw = 75 700; Mn = 72 300; Mw/Mn = 1.05.
Non reacted lactide: 2 %
Non reacted glycolide: <0.4 %
Mol ratio glycolide/lactide in the polymeric chains: 47/53
NMR and IR: As in Example 1.

Examples 11-12
In an analogous manner as described in Example 3, the following polyol esters were prepared:

Ex.	polyol	Dl-di-lactide	di-gly-colide	Sn-octoate	react. temp.	Mw / Mn	Mw/Mn	mol ratio lactide/glycolide	acid number	non reacted lactide, glycolide
11	0.63 g β-cyclo-dextrine	39.6g	26.1g	0.13ml	165.8°	16,200 5,100	3.18	54 46	1.7	<0.2 % <0.4 %
12	0.63g β-cyclo-dextrine dried at 120° in vacuo	39.6g	26.1g	0.13ml	163.9°	24,100 10,700	2.26	53 47	6.2	<0.2 % <0.4 %

Example 13

The product of Example 10 was treated in an analogous manner as described in Example 6. The filtration pressure was however raised to 3 atm.

Flow velocity 0.2 ml/min.

Residue

Mw = 72 200, Mn = 59 800, $\frac{Mw}{Mn}$ = 1.20

From NMR

$\frac{\text{lactide}}{\text{glycolide}} = \frac{53}{47}$ (mol ratio)

Acid number 1.0

Filtrate

Mw = 27 100, Mn = 15 500, $\frac{Mw}{Mn}$ = 1.75

From NMR

$\frac{\text{lactide}}{\text{glycolide}} = \frac{52}{48}$ (mol ratio)

Acid number 21.2

Example 14

The product of Example 10 was treated in an analogous manner as described in Example 6. The filtration pressure was however raised to 2 atm.

Flow velocity 0.3 ml/min

Residue

Mw = 76 700, Mn = 72 300, $\frac{Mw}{Mn}$ = 1.06

Filtrate

Mw = 67 900, Mn = 47 600, $\frac{Mw}{Mn}$ = 1.43

Example 15

Equal amounts of the residues of the Examples 13 and 14 lead, after intermediate dissolution in methyl ne dichloride, to a mixture of the following formation:

Mw = 70 000, Mn = 51 600, $\frac{Mw}{Mn}$ = 1.36

Examples 16 - 17 Polyol ester from D(−)mannitol, DL-dilactide and di-glycolide
In an analogous manner as described in Example 1, the following polyol esters were prepared:

Ex.	polyol	DL-di-lactide	digly-colide	Sn-octoate	react. temp.	Mw Mn	$\frac{Mw}{Mn}$	Mol ratio $\frac{\text{lactide}}{\text{glycolide}}$	Acid number	non reacted lactide and glycolide
16	0.1g D(−) mannitol (0.2%)	30.15g	19.85g	0.25 ml	177.5°	23,500 13,200	1.78	54 46	6.2	<0.1 % <0.4 %
17*	5.0g D(−)-mannitol (10 %)	30.15g	19.85g	0.25 ml	176.5°	3,500 3,000	1.13	54 46	1.4	<0.2 % <0.4 %

* for analytical purposes, see further comments.

Examples 18 - 23 Polyol esters from other polyols, DL-dilactide and diglycolide
In an analogous manner as described in Example 1, the following polyol esters were prepared:

Ex.	polyol	DI-di-lactide	digly-colide	Sn-octoate	react. temp.	Mw Mn	Mw/Mn	Mol ratio lactide/glycolide	acid number	non reacted lactide and glycolide
18	0.5 g penta-erythritol (1%)	30.15g	19.85 g	0.25 ml	132.5°	14,800 10,000	1.49	54 46	7.6	0.4 % 0.1 %
19*	5 g penta-erythritol (10%)	30.15g	19.85 g	0.25 ml	154.5°	2,740 2,450	1.12		0.73	
20	0,1 g sorbi-tol (0.2%)	30.15g	19.85 g	0.25 ml	179.1°	35,600 20,500	1.74	57 43		
21	0.1 g ribitol (0.2%)	30.15g	19.85 g	0.25 ml	159.7°	16,080 6,800	2.38			<0.1 % <0.4 %
22	0.1 g xylitol (0.2%)	30.15g	19.85 g	0.25 ml	156.6°	15,600 6,000	2.60			<0.1 % <0.4 %
23	0.1 g D(−)-fructose (0.2%)	30.15g	19.85 g	0.25 ml	175°	21,900 12,700	1.73	54 46		

* for analytical purposes see comments after

Comments on Example 17

NMR (in $CDCl_3$)

δ (ppm) 5.23 (m, -*CH*- of lactic acid, 1H); 4.83 (m, -CH_2- of glycolic acid, 1.73 H); 4.46 - 4.17 (m, -*CH*- and -CH_2- of mannitol and of the terminal lactic- or glycolic acid units.

Mol ratio: lactide/glycolide/mannitol = 1:0.86 : 0.08. This corresponds to a Mw of 1530 (however in the signal 4.46-4.17 are also included the terminal lactic- or glycolic acid units).

Used amount mannitol 672×10^{-4} Mol%; incorporated amount 526×10^{-4} Mol%.

Comments on Example 19

NMR (in $CDCl_3$)

δ (ppm) 5.23 (m, -*CH*- of lactic acid, 1H); 4.9-4.65 (m, -CH_2 of glycolic acid, 1,5H); 4.45-4.10 (m, -CH_2- of pentaerythritol and -*CH*- and -CH_2- of the terminal lactic acid or glycolic acid units, 1H); 1.58 (m, CH_3 of lactic acid, 3H).

Mol ratio lactide/glycolide/pentaerythritol: 1:0.75:0.15 (however in the signal 4.45-4.10 are also included the terminal lactic- or glycolic acid units).

Used amount pentaerythritol 960×10^{-4} Mol%, incorporated amount (from NMR) = 1000×10^{-4} Mol% (the signals at 4.45-4.10 ppm do not exclusively relate to pentaerythritol).

Determination of the degradation of polyol ester in vitro

Example 24

30 to 80 µm thick films are moulded from 5% solutions of the polyol ester of Example 6 in methylene dichloride. The films are dried for 50 hours at 40° in vacuo, thereafter several days in an desiccator containing P_2O_5.

300 mg of the film, divided into little pieces were added to 30 ml of distilled water and shaken at 37° (50 rpm).

The amount of polymer was determined periodically by filtration and weighing.

Example 25

Implants in the form of tablets of 7 mm diameter and of 23 - 25 mg, pressed from a polyol ester granulate of Example 6 at 80 bar and 75° for 10 min., were implanted i.p. in rats. After a certain period they were extracted from the tissue with methylene dichloride, and thereby separated from organic tissue material, evaporated to dryness and weighed.

Release of active agents from polyol ester matrices in vitro

Example 26

Release tests were carried out with microcapsules, which contained bromocriptine as active agent. The microcapsules were prepared according to the above described spray drying method with the following parameters:

Bromocriptine mesylate	2.6 g
Matrixpolymer of Example 9 (residue)	10.0 g
Methylene dichloride	100 ml
Spray conditions (NIRO equipment)	
Temperature of the input	50°C
Temperature of the output	40°C
Air pressure	2 atm
Influx	32 ml/min

After their preparation the microcapsules were dried for 48 hours at 30° in a low vacuum, sieved (<180 um) and washed with citrate buffer at pH 3. The microcapsules contained 17.9 % of the active agent.

After repeated drying in low vacuum (48 hours, 35°, 0.1 bar) and sieving (<180 um) the microcapsules were gammasterilized at 2.5 Mrad.

The release was measured photometrically at 301 nm at 25°C in citrate buffer pH 4 as an extraction medium, poured freshly through the microcapsules with a flow velocity of 2.5 ml/min.

Over a period of 24 hours about 62 % of the active agent was regularly released.

N.B. The release in vitro was measured at pH 4 because of better solubility of bromocryptine at this pH.

Example 27

Release tests were carried out with microcapsules, which contained codergocrine as a active agents.

The microcapsules were prepared according to the above described emulsion process with the following parameters:

Codergocrine base	7 g
Matrix polymer of example 5	13 g
Methylene dichloride	40 ml
Ethanol 94%	30 ml

Emulsifying conditions:

Volume ratio organic phase/aqueous phase: 1:65
Rotation speed of the turbine p = 3100 rpm

The release was measured as described in Example 26.

Example 28

The process of Example 27 was carried out with the following parameters:

Ketotifen base	5 g
Matrix polymer of example 5	15 g
Methylene dichloride	80 ml

Emulsifying conditions:

Volume ratio organic phase/aqueous phase: 3:130 p = 2000 rpm
Stirring time: 2 hours
The microcapsules contained 16.5 % Ketotifen.

Example 29 Release of active agents from polyol ester matrices in vivo

Release tests were carried out with microcapsules, which contained bromocriptine as active agent.

The microcapsules were prepared according to the above described spray drying process in the NIRO-spray drying apparatus, equipped with a centrifugal spray gun. The matrix polymer consisted of the product of Example 4 and contained 17.8 % bromocriptine.

An amount of these microcapsules, corresponding to 5.0 mg bromocriptine-mesylate, in a vehicle of 0.2 ml of sodium carboxymethylcellulose, was injected in the right thigh muscle of a rabbit. Periodically blood was taken from the rabbit during 21 days.

The blood levels of the medicine were measured by a specific radioimmunoassay and had a mean value of 1.6 ng/ml (A.U.C. = 33.0). The blood levels were practically all between 1.20 and 1.80 ng/ml.

CLAIMS

1. An ester of polyol, said polyol containing at least 3 hydroxyl groups and having a molecular weight of up 20,000 at least 1 hydroxyl group in said polyol being in the form of an ester, with a poly- or co-poly-lactic acid residue each having a molecular weight of at least 5,000.

2. A reaction product of a polyol containing at least 3 hydroxyl groups and having a molecular weight of up to 20,000 or a reactive derivative thereof and lactic acid or a reactive derivative thereof and if desired at

least a second hydroxycarb xylic acid or a functional derivative thereof, th product having a p lymer chain of molecular weight f at least 5,000.

3. A product according to claim 1 or 2, in which the poly l is the linear polyol mannitol, p ntaerythritol, sorbitol, ribitol or xylitol.

4. A product according to claim 1 or 2, in which the polyol is a polyol with 6 hydroxyl groups.

5. A product according to claim 1 or 2, in which the polyol is a polyol with a cyclic structure and with 4 to 30 hydroxyl groups.

6. A product according to claim 5, in which the polyol is a polyol with one or more monosaccharide units with at least 3 hydroxyl groups per unit.

7. A product according to claim 6, in which the polyol is a polyol with fructose structure.

8. A product according to claim 7, in which the polyol is a polyol, which comprises one fructose unit.

9. A product according to claim 1 or 2, in which the polyol is a polyol with glucose structure.

10. A product according to claim 9, in which the polyol is a polyol, which comprises one gluclose unit.

11. A product according to claim 9, in which the polyol is a polyol, which comprises 2 to 8 glucose units.

12. A product according to claim 11, in which the polyol is a polyol, in which the glucose units are connected in 1, 4 and/or 1,6-position.

13. A product according to claim 12, in which the polyol is a polyol, in which the glucose units are connected in the 1,4-position.

14. A product according to claim 13, in which the polyol is a polyol, which comprises one β-cyclodextrine unit.

15. A product according to any preceeding claim, with acid residues, comprising 30 to 70 Mol% of glycolic acid units.

16. A product according to any preceeding claim, with acid residues comprising up to 20 Mol% of ε-hydroxycapronic acid units.

17. A product according to any preceeding claim, wherein, having at least 2 ester chains, each of the chains comprise the same hydroxycarboxylic acid residues.

18. A product according to any preceeding claim, wherein in the GPC any separate low molecular weight peak comprises altogether up to 10% of the height of the peak Mw of the polyester.

19. A process for the production of the product of any preceeding claim, characterised in that a polyol of a molecular weight of up to 20,000 and having at least 3 hydroxyl groups or a reactive derivative thereof is esterified with lactic acid or a reactive derivative thereof and if desired with at least a second hydroxycarboxylic acid, or a functional derivative thereof.

20. A process for the production of the product of claim 1, characterised in that a polyol of a molecular weight of up to 20,000 and having at least 3 hydroxyl groups, is reacted with lactic acid or additionally with at least a second hydroxycarboxylic acid in lactone- or dimeric cyclic ester form, in the presence of a catalyst, for facilitating a ring opening polymerisation.

21. A process according to claim 19 or 20, characterised in that at least some of the low molecular weight parts are removed from the product.

22. A process according to claim 21, characterised in that the product is subjected to membrane filtration.

23. A process for the production of a product according to claim 1, substantially as hereinbefore described with reference to any one of the Examples.

24. A product produced by any one of claims 19 to 22.

25. A product according to any claims 1 to 18 and 24 for use as a depot matrix material.

26. A depot matrix material of a product according to any claims 1 to 18 and 24, containing a pharmacologically active compound.

27. A depot matrix material of a product according to claim 26, containing bromocriptine, ketotifen, or co-dergocrine as a pharmaceutically active agent.

28. A parenteral pharmaceutical depot formulation for use as an implant or microcapsules containing a pharmacologically active agent embedded or encapsulated in a polymer matrix, said formulation being adapted to release all or substantially all the active material over an extended period of time and the poiymer being adapted to degrade sufficiently to be transported from the site of administration within 20 days after release of all or substantially all the active agents.

29. Composition according to claim 28, containing bromocriptine, ketotifen or co-dergocrine as a pharmaceutically active agent.

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